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1623

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Dipak K. Banerjee, *et al.*	Group Art Unit: 1623
Application. Number: 09/779,447	Examiner: Howard V. Owens, Jr.
Filed: February 9, 2001	
For: METHODS FOR INHIBITING ANGIOGENESIS	**REPLY BRIEF**

Appellants respectfully submit this reply to the examiner's Answer Brief mailed January 13, 2005.

ARGUMENT

I. The Prior Art Relied Upon by the Examiner Teaches Away from Administering Tunicamycin to a Patient.

Banerjee 1993 investigated the basic biologic link between glycosylation and angiogenesis. Banerjee 1993 successfully demonstrated that these two processes were linked. In demonstrating this connection, Banerjee 1993 disclosed various experiments including one showing that tunicamycin inhibited glycosylation. Banerjee 1993 did not, however, take the further step attempting to inhibit angiogenesis in a patient by administration of tunicamycin.

Although this is undisputed by the examiner, he contends that this step would have been obvious to try in view of Banerjee 1993 and in further view of Tiganis 1992. The examiner's argument errs on the specific teachings of Tiganis 1992 and on the teachings of the prior art when viewed as a whole. The two paragraphs of Tiganis 1992 at issue read:

> One situation where a glycoproteins are likely to be absolutely essential for maintaining permeability, albeit totally restricted, is in those vessels which have tight junctions and serve as a barrier function. Since a feature of tunicamycin toxicity in animals is impaired permeability of brain microvessels an important question is whether tunicamycin has a direct effect on micorovessels *in vivo* and if so whether glycoprotein components of the tight junctions (zonula occludens) are specifically

> altered. Although direct effects of tunicamycin on glycoproteins of endothelial cells *in vivo* have not been studied, low dose intraperitoneal administration of tunicamycin in the rat modifies the synthesis of small intestine brush border membrane glycoproteins. Consequently first pass metabolism of tunicamycin in the liver was insufficient to prevent systemic delivery of tunicamycin to the intestine.
>
> In view of this finding and because endothelial cells have proved to be so vulnerable to tunicamycin *in vitro*, the damage to brain microvessels in tunicamycin-treated animals is likely to be due to a direct action of tunicamycin on the endothelial cells. Although the precise molecular components of tight junctions are not known, the glycoprotein CAM uvomorulin plays an important role in the assembly and maintenance of tight junctions in epithelial cell monolayers and either uvomorulin or a related CAM may be the target molecule for tunicamycins effects on brain microvessels. Now that tight junctions have been shown to form in cocultures of astrocytes and endothelial cells, it should be possible to use tunicamycin to examine the role of glycoproteins in the assembly and turnover of the molecular components of tight junctions in this co-culture system.

Page 199, column 2, ¶¶1-2 (citations omitted, underlining supplied). From these paragraphs the examiner somehow concludes that Tiganis 1992 taught that tunicamycin was not toxic when administered at low levels, but only at toxic levels. (Answer Brief at p. 7.) The problem with this argument is that it is totally unsupported by the subject paragraphs. It is nothing more than speculation by the examiner. Stepping back in time, Banerjee 1993 and Tiganis 1992 fairly teach that tunicamycin inhibits glycosylation and that there is an undefined link between glycosylation and angiogenesis. These same references, however, also teach away from the administration of tunicamycin to a patient due to concerns of brain damage. Because the claims on appeal expressly recite administration of tunicamycin to a patient, these references teach away from the invention.

II. Even if Banerjee 1993 and Tiganis 1992 Had Suggested the Administration of Tunicamycin to Inhibit Angiogenesis (which They Do Not for the Reasons Set Forth Above), Neither Teaches or Fairly Suggests a Resting Period to Improve the Effectiveness of Treatment as Recited by the Claims on Appeal.

Even accepting the examiner's erroneous reading of the prior art references upon which his rejection relies, these reference neither teach nor in any way suggest the administration followed by a resting period followed by the re-administration of tunicamycin,

as expressly recited in the claims on appeal. The examiner completely fails to identify any teaching in any prior art reference that treatment by tunicamycin would benefit by the claimed resting period. Absent any evidence of such a teaching in the prior art, the examiner has failed to establish a *prima facie* case of obviousness. The claims stand in condition for allowance.

III. Examiner's Reliance upon *In re Brana* Is Misplaced.

The examiner relies upon *In re Brana*, 51 F.3d 1560, for determining what is necessary to enable one skilled in the art. The examiner, however, has not made any rejection under 35 U.S.C. § 112 and so appears to concede that the specification enables the claims. Consequently, this is not an issue on appeal because no rejection has been made under 35 U.S.C. § 112.

CONCLUSION

For the reason set forth above and in appellant's Opening Brief, it is respectfully submitted that the cited references fail to teach or fairly suggest the claimed invention. In fact the cited references teach away from the claimed invention. Accordingly, the subject claims stand in condition for allowance and the examiner's rejection should be reversed.

Respectfully submitted,

Date: 2/22/05

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Commissioner for Patents
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Sir:

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- Reply Brief

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